Psychoneuroendocrinology (2009) 34, 110—117

available at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/psyneuen

Androgen treatment effects on memory in female-to-male transsexuals

Esther Gómez-Gil [a,*], Silvia Cañizares [b], Ana Torres [b], Fernanda de la Torre [b], Irene Halperin [c], Manel Salamero [b]

[a] Department of Psychiatry, University of Barcelona, Institute of Neurosciences, Hospital Clinic, Barcelona, Spain
[b] Department of Clinical Psychology, University of Barcelona, Institute of Neurosciences, Hospital Clinic, Barcelona, Spain
[c] Department of Endocrinology, University of Barcelona, Hospital Clinic, Barcelona, Spain

Received 9 May 2008; received in revised form 21 July 2008; accepted 21 August 2008

KEYWORDS
Androgen;
Sex hormones;
Transsexual;
Gender identity disorder;
Memory;
Cognition

Summary
Introduction: It has been hypothesized that cognitive and memory-related brain function in transsexuals during cross-sex hormonal treatment might be activated towards that of the subjective gender. However, research on this topic has produced inconsistent results, and to the best of our knowledge no studies have investigated memory changes in androgen-treated female-to-male (FM) transsexuals.
Methods: A total of 33 FM transsexuals underwent neuropsychological testing in order to examine the effects of androgen on memory. We used a longitudinal design in which 14 FM transsexuals were tested twice, before and after receiving 6 months of testosterone treatment. In addition, a cross-sectional design was used to compare 10 individuals off treatment versus 9 individuals on testosterone treatment for at least 6 months.
Results: Participants tested before and after 6 months of androgen treatment improved significantly their performance on a visual memory task (visual paired associates, immediate recall, WMS-R). The cross-sectional design confirmed that patients on androgen treatment for at least 6 months performed better than subjects off treatment on the same task and also on another visual memory task (Rey—Osterrieth complex figure test, ROCF; copy and delayed recall). No differences were found in any verbal memory test for either design.
Conclusions: The results indicate that androgen has an influence on visual memory, but not on verbal memory. Therefore, for FM transsexuals the data support an activating effect for androgens on visual memory, a domain that generally tends to favour males.

1. Introduction

Although men and women do not differ in general intelligence, sex differences in some cognitive functions have been widely established in the literature. Men tend to

* Corresponding author at: Department of Psychiatry, Instituto de Neurociencias, Hospital Clínic, Villarroel 170, 08036 Barcelona, Spain. Tel.: +34 93 2275477; fax: +34 93 2275477.
E-mail address: esgomez@clinic.ub.es (E. Gómez-Gil).

0306-4530/$ — see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.psyneuen.2008.08.017

outperform women on some visuo-spatial tasks (Linn and Petersen, 1985). In contrast, women generally perform better than men on verbal fluency (Halpern, 1992) and perceptual speed tasks (Mann et al., 1990). A similar pattern of differences has also been described in regard to memory, another cognitive domain. Females tend to excel on certain verbal memory tasks, such as verbal learning and story recall tests (Bleecker et al., 1988; Basso et al., 2000), whereas males generally excel on certain visual memory tests, such as reproducing designs from memory (Basso et al., 2000; Lewin et al., 2001). Nevertheless, there is a considerable overlap in cognitive performance between men and women, and it is difficult to find sex differences in small populations (Kimura, 1996, 2002; Torres et al., 2005). In fact, the most stable sex difference found in many studies of normal populations is on mental rotation tasks, which favours men (Hampson, 1995).

It has been suggested that these cognitive differences are related to sex hormonal mechanisms. In this regard it has been proposed that endogenous sex hormones, estrogen or androgen, affect cognitive functioning through both pre- and perinatal permanent organisational effects on brain structures, as well as through the reversible postnatal activational effects that are thought to occur during puberty or in adulthood (Hampson, 1995; Kimura, 2002).

The possible activational effects of androgen on cognitive functioning have not, however, been widely reported. In men, experimental studies suggest beneficial changes in cognitive function induced by testosterone supplementation (Shute et al., 1983; Gouchie and Kimura, 1991; Moffat and Hampson, 1996; Barret-Connor et al., 1999; Cherrier et al., 2007). Moreover, higher free testosterone levels have been related to better visuo-spatial abilities and semantic memory (Sherwin, 2003; Thilers et al., 2006). In women, the available data suggest that high testosterone levels are associated with better performance on mental rotation and visuo-spatial abilities (Shute et al., 1983; Imperato-McGinley et al., 1991; Gouchie and Kimura, 1991; Moffat and Hampson, 1996; Hausmann et al., 2000; Aleman et al., 2004), and that they have a negative influence on verbal fluency and verbal memory (Hogervorst et al., 2004; Thilers et al., 2006; Schattmann and Sherwin, 2007). However, inconsistent results have been obtained both in women (Wolf and Kirschbaum, 2002; Hines et al., 2003; Halari et al., 2005; Malouf et al., 2006; Shah et al., 2006) and in men (McKeever et al., 1987; Wolf et al., 2000; O'Connor et al., 2001; Wolf and Kirschbaum, 2002; Kenny et al., 2004; Halari et al., 2005). Further research is needed to establish whether androgen hormones have an activational influence on cognitive functions in men and women.

Transsexual patients are interesting model for investigating the effects of varying hormonal levels on cognitive function because they receive supraphysiological doses of cross-sex hormonal treatment in the course of the sex reassignment procedure. Transsexualism (ICD Classification of Mental and Behavioural Disorders, ICD-10), also known as gender identity disorder (GID) of adulthood or adolescence (diagnostic and statistical manual of mental disorders, DSM-IV-TR), is characterized by a strong and persistent cross-gender identification, accompanied by persistent discomfort with the biological sex or sense of inappropriateness in the gender role of that sex (American Psychiatric Association, 2000), and it is usually accompanied by the wish to make the body as congruent as possible with the preferred sex through hormone treatment and sex reassignment surgery (World Health Organization, 1993). As part of their sex reassignment, female-to-male (FM) transsexuals are treated with androgens to promote masculinization and male-to-female (MF) transsexuals are treated with estrogens in combination with antiandrogens to promote feminization (Gómez-Gil and Esteva de Antonio, 2006). After 3 months of hormone treatment, sex hormone levels of transsexuals are in the range of those of the opposite sex (Meyer et al., 1986).

Studies investigating cognitive changes in transsexual patients receiving hormonal treatment are scarce and have produced inconsistent results. A number of studies have provided support for the idea that cross-sex hormone treatment skews the cognitive performance of transsexual patients towards the pattern of the desired sex. For instance, in MF patients, Van Goozen et al. (1995) found impaired visuo-spatial abilities and an improvement on some verbal fluency tasks after receiving cross-sex hormones. However, the deleterious effect on visuo-spatial functions was not replicated in several longitudinal studies (Slabbekoorn et al., 1999; Van Goozen et al., 2002; Haraldsen et al., 2005; Miles et al., 2006) or in studies with normal controls (Wisniewski et al., 2005). Similarly, in FM patients, initial studies reported improved visuo-spatial performance (Van Goozen et al., 1994, 1995; Slabbekoorn et al., 1999) and impaired verbal fluency (Van Goozen et al., 1994, 1995) after 3 or more months of testosterone treatment. These findings could not, however, be replicated in subsequent studies for either visuo-spatial abilities (Van Goozen et al., 2002; Haraldsen et al., 2005) or verbal fluency (Slabbekoorn et al., 1999; Haraldsen et al., 2005).

Memory functioning has received little attention in research on cognition in transsexual patients. Cohen-Kettenis et al. (1998) found in transsexuals who were not yet hormonally treated that FM patients performed worse on a verbal learning task than the female control group, whereas MF patients obtained better results than did the male control group. Miles et al. (1998) compared MF transsexuals taking estrogens with a transsexual control group awaiting treatment and reported that the former showed enhanced performance on a verbal learning test. However, in a recent study by the same authors these results were not replicated (Miles et al., 2006). A study about visual memory in a sample of MF patients receiving cross-sex hormone treatment did not find any differences with respect to male controls (Wisniewski et al., 2005). Similarly, Miles et al. (2006) failed to find a deleterious effect of estrogenic treatment on several visual memory tests in MF transsexuals. To our knowledge, there are no studies about changes in memory functioning in FM transsexuals receiving androgenic treatment.

The aim of the present study was to examine the effects of androgens on memory in FM transsexuals. We used a longitudinal design in which FM transsexuals were tested twice, before and after 6 months of androgen treatment. We also used a cross-sectional design to compare groups of individuals on versus off androgen treatment. The hypothesis was that FM transsexuals receiving androgens would show enhanced visual memory and impaired verbal memory.

2. Methods

2.1. Sample

The sample comprised 33 FM transsexual volunteers recruited through the Gender Identity Unit of the Hospital Clinic of Barcelona. This public hospital is the only centre providing specialized and comprehensive psychiatric, psychological and endocrine therapy for transsexual patients in Catalonia, although surgical treatment is only available privately in this region. Diagnostic assessment of GID in adulthood or adolescence or transsexualism was formulated according to the revised fourth edition of the diagnostic and statistical manual of mental disorders (DSM-IV-TR; American Psychiatric Association, 2000) and the tenth revision of the international classification of diseases (ICD-10; World Health Organization, 1993). The diagnosis was made after several sessions with two mental health professionals (psychiatrist and psychologist). We use semi-structured, sociodemographic, clinical and psychiatric interviews (Gómez-Gil et al., 2008). The unit has adopted the standards of care guidelines of the World Professional Association for Transgender Health (Meyer et al., 2001).

All subjects were informed that the purpose of the study was to investigate the effects of hormone fluctuations on certain psychological functions; none of them was aware of the specific nature of our hypotheses. The study was approved by the Ethics Committee of the Hospital Clinic of Barcelona and was conducted in accordance with the Declaration of Helsinki. Participants provided written informed consent, and were not paid for taking part in the study.

A longitudinal design was used with a sample of 14 participants, who were tested before and 6 months after hormonal treatment. The samples for the subsequent cross-sectional design consisted of 9 patients who were off androgen treatment (testosterone naive) and 10 patients on androgen treatment for at least 6 months at the time tested. Patients in the cross-sectional study formed an independent sample from the one used in the longitudinal design. Age and years of education of the samples are shown in Table 1.

All participants were early-onset gender nonconformity (before puberty), erotically attracted to females, right-handed in writing, and in good physical health. Participants had no endocrine, neurological or major psychiatric comorbidity and were free of medication that could affect cognitive functioning. The general intellectual ability of participants was estimated by their score on the vocabulary factor of the Primary Mental Abilities tests (PMA rev., Thurstone and Thurstone, 1962, 1989) and according to their educational level.

2.2. Cognitive tests

Four tests of known clinical utility were selected to tap several aspects of visual and verbal memory.

(a) Verbal memory tests

Logical memory (Wechsler Memory Scale-Revised, 1987): The examiner reads two stories, stopping after

Table 1 Main characteristics of the transsexual patients

	Longitudinal design (n = 14)	Cross-sectional design		F	p-Value[a]
		Off androgen treatment (n = 9)	On androgen treatment (n = 10)		
Demographical characteristics					
Age	27.43 (9.28)	23.78 (5.67)	27.7 (5.44)	.85	.437
Vocabulary test (PMA)[b]	25.86 (10.9)	22.33 (12.96)	29.4 (7.76)	1.03	.368
Education (years)	11.79 (3.45)	12.33 (3.71)	12.8 (2.62)	.281	.757
	Longitudinal design (n = 14)	Cross-sectional design		Z	p-Value[c]
		Off androgen treatment (n = 9)	On androgen treatment (n = 10)		
Hormonal testing					
Total T (ng/dl)					
Off	54.26 (20.65)	48.64 (12.05)		−.096	.923
On	1012.78 (739.52)		517.26 (295.15)	−1.015	.310
Free T index (%)					
Off	4.61 (3.25)	2.54 (1.77)		−1.637	.102
On	108.59 (86.34)		68.74 (62.29)	−.839	.402

Note: means and standard deviations are shown. PMA, primary mental abilities test; T, testosterone; off, off androgen treatment; on, on androgen treatment.

[a] p-Values are from three univariate ANOVAs.

[b] Results are expressed in raw scores.

[c] p-Values are from the Mann–Whitney U-test.

each reading for an immediate free recall. After a delay of 30 min another free recall of the stories is requested. The score consists of one point for each unit of information correctly recalled, and the measures obtained are immediate recall and delayed recall. The maximum score for each measure is 50.

Verbal paired associates (Wechsler Memory Scale-revised, 1987): This is a word-learning test with built-in cueing. A list of eight word pairs is presented (four easy to associate and four hard to associate) and then the first word of each pair is read to the subject to give the associated second word. There are three to six trials of immediate recall, depending on the subject's learning, but scoring is only based on the first three trials (measure of immediate recall). A trial is then presented after a delay of 30 min (measure of delayed recall). The word-pairs are randomized in each trial in order to prevent positional learning. Each correct recall scores one point. The maximum score for immediate recall is 24 and for delayed recall 8.

(b) Visual memory tests

Visual paired associates (Wechsler Memory Scale-revised, 1987): With a format that parallels that of verbal paired associates, the examinee is shown six nonsense line drawings, each paired with a different colour with a 3 s exposure. The subject then sees the designs in a different order for each trial and must provide the colour that goes with it. There are three to six trials of immediate recall, depending on the subject's learning, but scoring is only based on the first three trials (measure of immediate recall). A trial is then presented after a delay of 30 min (measure of delayed recall). One point is scored for a correctly recalled pair. The maximum score for immediate recall is 18 and for delayed recall 6.

Rey—Osterrieth complex figure test (ROCF) (Rey, 1941, 1999; Osterrieth, 1944): A complex geometric form is presented to the subject, who is instructed to copy the figure on paper as accurately as possible. After a delay of 30 min the subject is requested to recall the figure (measure of delayed recall). Each element of the figure is scored in terms of accuracy and correct location for the copy and memory trials. Maximum score for each trial is 36.

2.3. Procedure

The cognitive assessment was carried out individually by two graduate psychologists with experience in test administration and scoring. The procedure typically lasted 1 h. In the longitudinal design, patients were tested twice, before starting hormone treatment and 6 months after it began. We chose a 6-month post-test evaluation point in order to ensure a stable level of sex hormone. In the cross-sectional design, subjects were only tested once.

2.4. Hormone treatment

The androgen administration schedule was very heterogeneous within the group, and frequently defined by patients' personal preferences. Patients received either intramuscular injections of depot testosterone esters every 2—4 weeks, or daily transdermal testosterone as patches or gel. In spite of this variability, the doses used were those usually recommended for testosterone replacement in male hypogonadal subjects. Serum total testosterone and free testosterone index were determined every 3 months, and androgen doses were modified, when necessary, in order to keep the levels within normal range for adult males. Hormonal testing was performed not more than 2 weeks before or after the cognitive assessment for all patients. Testosterone was analyzed by a competitive enzyme immunometric assay (Immuno-1, Bayer), with sensitivity 0.05 ng/dl and 11%, 3% and 6% variation coefficients for controls with mean levels of 86, 826 and 1580 ng/dl, respectively. Normal levels (5—95% percentiles) are 10—80 ng/dl for adult females and 275—850 ng/dl for males. Free testosterone index was calculated from total testosterone and sex steroid binding globulin concentrations using a mass action equation. Normal levels (5—95% percentiles) are 1—7% in female subjects, and 50—140% in male subjects.

2.5. Statistics

Data were analysed using the SPSS V.14.0 statistical software package for Windows. Raw scores were used for all the analyses of cognitive measures. In order to determine whether the subjects of the two designs (longitudinal and cross-sectional) were comparable we analysed the demographic and intellectual characteristics of the three independent samples by means of three univariate ANOVAs, and hormonal testosterone levels by the Mann—Whitney *U*-test because of the heterogeneity of the variances. The cognitive measures in the longitudinal design was analysed using the two-tailed Student's *t*-test for dependent samples for each cognitive measure, while for the cross-sectional design we used the two-tailed Student's *t*-test for independent samples. Effect size was measured by Cohen's *d* (1988). In behavioural science research, *d* values of 0.2 are considered small, those of 0.5 moderate, and those of 0.8 or greater as large values (Cohen, 1988). The level of significance was set at $p < .05$.

3. Results

3.1. Demographical characteristics and plasma testosterone levels

Patients included in the longitudinal and cross-sectional designs were similar in terms of age (F (2,30) = .85, p = .437), general intellectual ability (F (2,30) = 1.03, p = .368), and years of education (F (2,30) = .281, p = .757) (Table 1). The performance of the three study groups on the PMA vocabulary factor was in the low-average range; most subjects in the three samples had completed secondary education.

As expected, testosterone levels were within the normal range for female subjects both in the initial determination of the longitudinal study (before starting testosterone administration) and in the cross-sectional study in subjects off androgen treatment (Table 1). No significant differences were found either in serum total testosterone (Z = —.096, p = .923) or in free testosterone (Z = —1.637, p = .102) between them.

Table 2 Performance on memory tests for female-to-male transsexuals tested before and after 6 months of androgen treatment (longitudinal design)

Tests	Before treatment (n = 14)	After treatment (n = 14)	t	p-Value	Effect size
Logical memory I	28.61 (8.27)	29.93 (8.02)	−.94	.364	0.16
Logical memory II	24.68 (8.5)	27.79 (9.07)	−1.98	.070	0.37
Verbal paired assoc. I	19.64 (3.59)	20 (2.57)	−.50	.622	0.10
Verbal paired assoc. II	7.36 (.84)	7.42 (.65)	2.91	.775	0.07
Visual paired assoc. I	14.14 (2.82)	16.14 (2.14)	3.09	.009*	0.71
Visual paired assoc. II	5.5 (.76)	5.86 (.53)	−1.59	.136	0.47
ROCF, copy	33.64 (3.32)	32.43 (3.71)	1.21	.250	0.36
ROCF II	23.18 (5.64)	24.75 (6.19)	−1.62	.130	0.28

Note: means and standard deviations are shown. Results are presented as raw scores. Logical memory, verbal paired associates and visual paired associates are tests from the Wechsler memory scale-revised. ROCF (Rey–Osterrieth complex figure test). For all tests: I (immediate recall); II (delayed recall).

After 6 months' androgen therapy in the longitudinal study, and in patients from the cross-sectional study who were on androgen treatment, testosterone levels were within normal range for male subjects (Table 1). No significant differences were found either in serum total testosterone (Z = −1.015, p = .310) or in free testosterone (Z = −.839, p = .402) between them. The duration of hormonal treatment in the cross-sectional design ranged between 6 and 84 months (mean = 31.8; S.D. = 25.96).

3.2. Longitudinal study

In general, the post-hormonal treatment assessment showed a small increase in all the cognitive measures (Table 2). However, despite the potential learning effect, participants only improved significantly on one visual memory test, i.e. visual paired associates (WMS-R)—immediate recall (t = −3.09, p = .009) after 6 months of androgen treatment. The effect size was considered moderate (d = .71). There were no significant differences on any verbal memory test (logical memory, verbal paired associates, immediate and delayed recall), nor on any measures of the ROCF (copy and delayed recall).

3.3. Cross-sectional study

As shown in Table 3, participants on androgen treatment performed significantly better than subjects off treatment on several visual memory tests: visual paired associates, immediate recall (WMS-R) (t for unequal variances = −2.25, p = .048) and ROCF delayed recall (t = −2.86, p = .011). Patients on hormonal treatment also achieved significantly higher scores for copy accuracy on the ROCF. The effect sizes were considered large. There were no significant differences between groups for any verbal memory task.

4. Discussion

To the best of our knowledge the effect of chronic androgen treatment on visual and verbal memory has not been previously studied in FM transsexuals. The hypotheses tested were that FM transsexuals taking androgens would show enhanced visual memory and impaired verbal memory. Participants in the longitudinal study, tested before and after 6 months of androgen treatment, improved their performance on only one visual memory test, visual paired associates immediate recall. Secondarily, in the cross-sectional study, participants on androgen treatment scored higher not only on the same visual memory task (visual paired associates, immediate recall), but also on other visual memory tests (ROCF delayed recall) and on ROCF copy. As in the longitudinal study, no differences were found on verbal memory tasks. The three groups of patients were comparable with respect to potential confounding factors such as hand preference, sexual orientation, age, educational level, and

Table 3 Performance on memory tests for FM transsexuals tested when off and on androgen treatment (cross-sectional design)

Tests	Off hormonal treatment (n = 9)	On hormonal treatment (n = 10)	t	p-Value	Effect size
Logical memory I	27.11 (6.86)	29.55 (9.56)	−.63	.536	0.29
Logical memory II	22.50 (7.68)	25.65 (10.33)	−.75	.458	0.34
Verbal paired assoc. I	18.78 (3.03)	21.4 (2.63)	−2.02	.060	0.92
Verbal paired assoc. II	7.56 (.53)	7.50 (.85)	.17	.868	0.08
Visual paired assoc. I	13.78 (4.05)	17.00 (1.49)	−2.25	.048*	1.08
Visual paired assoc. II	5.78 (.67)	6 (.74)	−.99	.334	0.45
ROCF, copy	29 (4.70)	33.5 (2.37)	2.6	.024*	1.23
ROCF II	16.17 (5.71)	23.5 (5.46)	−2.86	.011*	1.31

Note: FM (female-to-male). Means and standard deviations are shown. Results are presented as raw scores. Logical memory, verbal paired associates and visual paired associates are tests from the Wechsler memory scale-revised. ROCF (Rey–Osterrieth complex figure test). For all tests: I (immediate recall); II (delayed recall).

general intelligence estimation. Moreover, individuals with any psychiatric, endocrine or neurological disorder were excluded. Therefore, these factors were not masking any androgen influence on memory performance. The results of our study thus suggest that at least 6 months of androgen treatment enhances visual memory but does not impair verbal memory in FM transsexuals. It is notable that despite the statistically significant improvement, the participants reported no clinically relevant effects on visual memory, even though the hormonal manipulation was very strong.

As regards visual memory, our findings of an improvement in this domain partly agree with early research that found a positive influence on visuo-spatial abilities in FM patients receiving cross-sex hormone treatment (Van Goozen et al., 1994, 1995; Slabbekoorn et al., 1999) but not with recent studies (Van Goozen et al., 2002; Haraldsen et al., 2005). Nevertheless, direct comparison of our results with these studies is not possible because we used visual memory tests, whereas previous research mainly tapped visuo-spatial abilities. Van Goozen et al. (1994, 1995) evaluated cognitive functioning in 35 FM transsexuals before and after 3 months of testosterone treatment and found that the administration of androgens was clearly associated with an improvement in visuo-spatial performance (two-dimensional rotated figures test). Slabbekoorn et al. (1999) studied the effects of testosterone manipulations on different cognitive domains (verbal, visual and motor) in 25 FM transsexuals tested before the onset of hormone treatment and after 3 and 10–12 months. They found that testosterone manipulations had a clear effect on spatial ability (three-dimensional rotated figures) after 3 months of testosterone treatment which persisted until 10 months, and even in a subsample of patients when they were off hormones for 5 weeks. Taken together, these results could suggest that androgen treatment has an activation effect on some cognitive functions. However, no additional evidence of such an activation effect has been reported. Van Goozen et al. (2002) compared 22 FM transsexuals with female and male controls but did not find any effect on the visuo-spatial ability of FM patients after a period of 14 weeks of androgen treatment. Recently, Haraldsen et al. (2005) studied the effects of intramuscular testosterone given every third week on several cognitive factors (rotation, visualization, perception, verbalization, logic and arithmetic) in 30 FM patients, assessed before and after 3 and 12 months of androgen treatment, and found that cross-sex hormone treatment failed to change any cognitive function in these patients. Overall, these conflicting results may be due to methodological issues, such as sample characteristics and differences in the cognitive tests employed.

As regards verbal memory, we found no changes after testosterone treatment. In the longitudinal design, effect sizes for measures of verbal memory were small (range: .07–.37), so it might be that a larger sample size than ours could detect some deleterious consequences of androgen treatment. To our knowledge, the effect of chronic androgen treatment on verbal memory in FM transsexuals has not been previously reported; prior research mainly tapped verbal fluency rather than verbal memory. Van Goozen et al. (1994) reported impaired verbal fluency, both oral and written, in FM patients with early-onset GID after 3 months of androgen treatment, although Slabbekoorn et al. (1999) and Haraldsen et al. (2005) were unable to replicate these findings.

Comparison of our study with other research studying androgens and memory in non-transsexual women is difficult, because the dosage of testosterone treatment in transsexuals is supraphysiological and may induce a different effect than in non-transsexual women.

In addition to an activational effect of androgen treatment on visual memory in FM transsexuals, an alternative explanation should be taken into account. The improvement in visual memory could also be secondary to the effect of estrogens. As suggested by Haraldsen et al. (2005), the sex hormones in cross-sex hormone treatment act on target cells that have not been previously exposed to such high levels of these hormones. Cross-sex testosterone treatment probably increases aromatization of testosterone to estrogens, and this may cause even higher estrogens levels in the brains of biological females (Krey et al., 1982). Since some studies have proposed that estrogens have a role in visual memory (Resnick et al., 1997; Smith et al., 2001) our positive results for visual memory could be attributed also to estrogens.

The present research does have some limitations. First, the sample sizes are small, which is why we used two separate designs (longitudinal and cross-sectional). Second, a positive unidirectional learning effect in the repeated measures design may be interpreted as a test/retest effect. Despite the absence of a control group for the longitudinal study, the cross-sectional design did allow inter-subject comparison, which confirmed the statistical significance of the longitudinal data and, moreover, identified some statistical significances in the same direction that were not detected in the longitudinal design. Third, although we controlled for variables which might have confounded our results (age, educational level, general intelligence, sexual orientation, early onset of GID, presence of psychiatric, endocrine or neurological disorder, or neuroactive treatment) there clearly could be other non-controlled variables affecting memory performance; examples would be the menstrual phase, the levels of testosterone at the same day of memory testing, and also the number of days since the last testosterone intramuscular injection in the 'on treatment' conditions. Nevertheless, Haraldsen et al. (2005) failed to find any relationship between changes in a number of endocrine parameters, including testosterone, after a cross-sex hormone treatment and an associated improvement in some cognitive measures. Finally, we did not use any mood scale for control purposes, and neither did we assess mood changes following androgen treatment in the test–retest design. Effects of cross-sex hormone treatment on emotionality in transsexuals have been described (for a review, see Slabbekoorn et al., 2001). However, none of our patients in either design reported clinical mood changes when the tests were performed. Other studies with a similar design in MF transsexuals treated with estrogens (Miles et al., 2006) have shown some positive mood changes, although the authors argued that is difficult to be certain that these observed changes were caused by estrogens itself rather than by other factors associated with the reasons for taking hormonal treatment, since the process of living as the desired sex may increase self-esteem and self-confidence. Future research must consider a larger sample and a more powerful repeated-measures design with a control group, which would allow more sophisticated statistical analyses to be applied.

In conclusion, the results of the present study indicate an activating effect of androgen treatment on some visual memory performance in FM patients. However, the effect was unlikely to be clinically appreciable. In addition, the current study suggests that verbal memory is not influenced by androgen treatment in FM transsexuals. If our findings are confirmed by independent studies, our data would also indicate the feasibility of studying transsexuals to address the question of whether androgen and estrogen act by activating cognitive brain function towards that of the subjective gender, in parallel with the endocrine and somatic changes observed during treatment.

Role of the funding source

No funding source has supported this study.

Conflict of interest

Co-authors do not have financial or personal conflicts of interest in this area.

Acknowledgements

We are grateful to the patients for their cooperation.

References

Aleman, A., Bronk, E., Kessels, R.P., Koppeschaar, H.P., Van Honk, J., 2004. A single administration of testosterone improves visuospatial ability in young women. Psychoneuroendocrinology 29, 612—617.

American Psychiatric Association, 2000. Diagnostic and Statistical Manual of Mental Disorders, 4th ed. DSM-IV-TR, Washington, DC.

Barret-Connor, E., Goodman-Gruen, D., Patay, B., 1999. Endogenous sex hormones and cognitive function in older men. J. Clin. Endocrinol. Metab. 84 (10), 3681—3685.

Basso, M.R., Harrington, K., Matson, M., Lowery, N., 2000. Sex differences on the WMS-III: findings concerning verbal paired associates and faces. Clin. Neuropsychol. 14, 231—235.

Bleecker, M., Bolla-Wilson, K., Agnew, J., Meyers, D., 1988. Age related sex differences in verbal memory. J. Clin. Psychol. 44, 403—411.

Cherrier, M.M., Matsumoto, A.M., Amory, J.K., Johnson, M., Craft, S., Peskind, E.R., Raskind, M.A., 2007. Characterization of verbal and spatial memory changes from moderate to supraphysiological increases in serum testosterone in healthy older men. Psychoneuroendocrinology 32, 72—79.

Cohen, J., 1988. Statistical Power Analysis for the Behavioral Sciences, 2nd ed. Lawrence Erlbaum Associates, Hillsdale, NJ.

Cohen-Kettenis, P.T., Van Goozen, S.H.M., Doorn, C.D., Gooren, L.J.G., 1998. Cognitive ability and cerebral lateralisation in transsexuals. Psychoneuroendocrinology 23, 631—641.

Gómez-Gil, E., Esteva de Antonio, I., 2006. Ser Transsexual (Being Transsexual). Editorial Glosa, Barcelona.

Gómez-Gil, E., Trilla, A., Salamero, M., Godás, T., Valdés, M., 2008. Sociodemographic, clinical, and psychiatric characteristics of transsexuals from Spain. Arch. Sex. Behav. doi:10.1007/s10508-007-9307-8.

Gouchie, C., Kimura, D., 1991. The relationship between testosterone levels and cognitive ability patterns. Psychoneuroendocrinology 16, 323—334.

Halari, R., Hines, M., Kumari, V., Mehrotra, R., Wheeler, M., Ng, V., Sharma, T., 2005. Sex differences and individual differences in cognitive performance and their relationship to endogenous gonadal hormones and gonadotropins. Behav. Neurosci. 119 (1), 104—117.

Halpern, D.F., 1992. Sex Differences in Cognitive Abilities. Erlbaum, New Jersey.

Hampson, E., 1995. Spatial cognition in humans: possible modulation by androgens and estrogens. J. Psychiatry Neurosci. 20, 397—404.

Haraldsen, I.R., Egeland, T., Haug, E., Finset, A., Opjordsmoen, S., 2005. Cross-sex hormone treatment does not change sex-sensitive cognitive performance in gender identity disorder patients. Psychiatry Res. 137, 161—174.

Hausmann, M., Slabbekoorn, D., Van Goozen, S., Cohen-Kettenis, P.T., Güntürkün, O., 2000. Sex hormones affect spatial abilities during the menstrual cycle. Behav. Neurosci. 114 (6), 1245—1250.

Hines, M., Fane, B.A., Pasterski, V.L., Mathews, G.A., Conway, G.S., Brook, C., 2003. Spatial abilities following prenatal androgen abnormality: targeting and mental rotation performance in individuals with congenital adrenal hyperplasia. Psychoneuroendocrinology 28 (8), 1010—1026.

Hogervorst, E., De Jager, C., Budge, M., Smith, A.D., 2004. Serum levels of estradiol and testosterone and performance in different cognitive domains in healthy elderly men and women. Psychoneuroendocrinology 29 (3), 404—421.

Imperato-McGinley, J., Pichardo, M., Gautier, T., Voyer, D., Bryden, M.P., 1991. Cognitive abilities in androgen-insensitive subjects: comparison with control males and females from the same kindred. Clin. Endocrinol. 34 (5), 341—347.

Kenny, A.M., Fabregas, G., Song, C., Biskup, B., Bellantonio, S., 2004. Effects of testosterone on behaviour, depression, and cognitive function in older men with mild cognitive loss. J. Gerontol. A: Biol. Sci. Med. Sci. 59 (1), 75—78.

Kimura, D., 1996. Sex, sexual orientation and sex hormones influence human cognitive function. Curr. Opin. Neurobiol. 6, 259—263.

Kimura, D., 2002. Sex hormones influence human cognitive pattern. Neuro. Endocrinol. Lett. 23 (Suppl. 4), 67—77.

Krey, L.C., Lieberburg, I., MacLusky, N.J., Davis, P.G., Robbins, R., 1982. Testosterone increases cell nuclear estrogen receptor levels in the brain of the Stanley—Gumbreck pseudohermaphrodite male rat: implications for testosterone modulation of neuroendocrine activity. Endocrinology 110, 2168—2176.

Lewin, C., Wolgers, G., Herlitz, A., 2001. Sex differences favoring women in verbal but not in visuospatial episodic memory. Neuropsychology 15, 165—173.

Linn, M.C., Petersen, N., 1985. Emergence and characterization of sex differences in spatial ability: a metaanalysis. Child. Dev. 56, 1479—1498.

Malouf, M.A., Migeon, C.J., Carson, K.A., Petrucci, L., Wisniewski, A.B., 2006. Cognitive outcome in adult women affected by congenital adrenal hyperplasia due to 21-hydroxylase deficiency. Horm. Res. 65 (3), 142—150.

Mann, V.A., Sasanuma, S., Sakuma, S., Masaki, S., 1990. Sex differences in cognitive abilities: a cross-cultural perspective. Neuropsychologia 28, 1063—1077.

McKeever, W.F., Rich, D.A., Deyo, R.A., Conner, R.L., 1987. Androgens and spatial ability: failure to find a relationship between testosterone and ability measures. Bull. Psychon. Soc. 25, 438—440.

Meyer III, W., Bockting, W.O., Cohen-Kettenis, P., Coleman, E., DiCeglie, D., Devor, H., et al., 2001. The Harry Benjamin gender dysphoria association's standards of care for gender identity disorders, sixth version. J. Psychol. Human Sex. 13, 1—30.

Meyer III, W.J., Webb, A., Stuart, C.A., Finkelstein, J.W., Walker, P.A., 1986. Physical and hormonal evaluation of transsexual patients: a longitudinal study. Arch. Sex. Behav. 15 (2), 121—138.

Miles, C., Green, R., Hines, M., 2006. Estrogen treatment effects on cognition, memory and mood in male-to-female transsexuals. Horm. Behav. 50, 708—717.

Miles, C., Green, R., Sanders, G., Hines, M., 1998. Estrogen and memory in a transsexual population. Horm. Behav. 34, 199—208.
Moffat, S.D., Hampson, E., 1996. A curvilinear relationship between testosterone and spatial cognition in humans: possible influence of hand preference. Psychoneuroendocrinology 21 (3), 323—337.
O'Connor, D.B., Archer, J., Hair, W.M., Wu, F.C.W., 2001. Activational effects of testosterone on cognitive function in men. Neuropsychologia 39 (13), 1385—1394.
Osterrieth, P.A., 1944. Le test de copie d'une figure complexe. Arch. Psychol. 30, 206—356.
Resnick, S.M., Metter, E.J., Zonderman, A.B., 1997. Estrogen replacement therapy and longitudinal decline in visual memory. A possible protective effect? Neurology 49 (6), 1491—1497.
Rey, A., 1941. L'examen psychologique dans les cas d'encéphalopathie traumatique. Arch. Psychol. 28, 286—340.
Rey, A., 1999. Test de copia y reproducción de memoria de una figura geométrica compleja. TEA, Madrid.
Schattmann, L., Sherwin, B.B., 2007. Testosterone levels and cognitive functioning in women with polycystic ovary syndrome and in healthy young women. Horm. Behav. 51, 587—596.
Shah, S., Bell, R.J., Savage, G., Goldstat, R., Papalia, M.A., Kulkarni, J., Donath, S., Davis, S.R., 2006. Testosterone aromatization and cognition in women: a randomized, placebo-controlled trial. Menopause 13 (4), 600—608.
Sherwin, B.B., 2003. Steroid hormones and cognitive functioning in aging men: a mini-review. J. Mol. Neurosci. 20 (3), 385—393.
Shute, V.J., Pelligrino, J.W., Hubert, L., Reynolds, R.W., 1983. The relationship between androgen levels and human spatial abilities. Bull. Psychon. Soc. 21, 465—468.
Slabbekoorn, D., Van Goozen, S.H.M., Megens, J., Gooren, L.J., Cohen-Kettenis, P.T., 2001. Effects of cross-sex hormone treatment on emotionality in transsexuals. I. J. Transgender. 5 (3), http://www.symposion.com/ijt/ijtvo05no03_02.htm.
Slabbekoorn, D., Van Goozen, S.H.M., Megens, J., Gooren, L.J.G., Cohen-Kettenis, P.T., 1999. Activating effects of cross-sex hormones on cognitive functioning: a study of short-term and long-term hormone effects in transsexuals. Psychoneuroendocrinology 24, 423—447.
Smith, Y.R., Giordani, B., Lajiness-O'Neill, R., Zubieta, J.K., 2001. Long-term estrogen replacement is associated with improved nonverbal memory and attentional measures in postmenopausal women. Fertil. Steril. 76 (6), 1101—1107.
Thilers, P.P., MacDonald, S.W.S., Herlitz, A., 2006. The association between endogenous free testosterone and cognitive performance: a population-based study in 35—90-year-old men and women. Psychoneuroendocrinology 31 (5), 565—576.
Thurstone, L.L., Thurstone, L.G., 1962. Primary Mental Abilities (Rev.) Science Research Associates, Chicago.
Thurstone, L.L., Thurstone, L.G., 1989. P.M.A. Aptitudes Mentales Primarias. TEA, Madrid.
Torres, A., Gómez-Gil, E., Vidal, A., Puig, O., Boget, T., Salamero, M., 2005. Diferencias de género en las funciones cognitivas e influencia de las hormonas sexuales (Gender differences in cognitive functions and influence of sex hormones). Actas Esp. Psiquiatr. 34, 408—415.
Van Goozen, S.H., Cohen-Kettenis, P.T., Gooren, L.J., Frijdas, N.H., Van de Poll, N.E., 1995. Gender differences in behaviour: activating effects of cross-sex hormones. Psychoneuroendocrinology 20 (4), 343—363.
Van Goozen, S.H., Slabbekorn, D., Gooren, L.J., Sanders, G., Cohen-Kettenis, P.T., 2002. Organizing and activating effects of sex hormones in homosexual transsexuals. Behav. Neurosci. 116 (6), 982—988.
Van Goozen, S.H., Cohen-Kettenis, P.T., Gooren, L.J.G., Frijda, N.H., Van de Poll, N.E., 1994. Activating effects of androgens on cognitive performance: causal evidence in a group of female to male transsexuals. Neuropsychologia 32, 1153—1157.
Wechsler, D., 1987. Wechsler Memory Scale-revised Manual. The Psychological Corporation, San Antonio, TX.
Wisniewski, A.B., Prendeville, M.T., Dobs, A.S., 2005. Handedness, functional hemispheric lateralization, and cognition in male-to-female transsexuals receiving cross-sex hormone treatment. Arch. Sex. Behav. 34 (2), 162—172.
Wolf, O.T., Kirschbaum, C., 2002. Endogenous estradiol and testosterone levels are associated with cognitive performance in older women and men. Horm. Behav. 41 (3), 259—266.
Wolf, O.T., Preut, R., Hellhammer, D.H., Kudielka, B.M., Schürmeyer, T.H., Kirschbaum, C., 2000. Testosterone and cognition in elderly men: a single testosterone injection blocks the practice effect in verbal fluency, but has no effect on spatial or verbal memory. Biol. Psychiatry 47 (7), 650—654.
World Health Organization (WHO), 1993. The ICD-10. Classification of mental and behavioural disorders. Diagnostic criteria for research, Geneva.